The paper by Rosmond et al in this issue of the *BMJ* (p 652) is a good example of this type of research.[10] The researchers investigated whether a specific variant of the gene encoding for the glucocorticoid receptor might influence the degree of abdominal obesity, and they also investigated the hormonal, metabolic, and haemodynamic disturbances associated with this phenotype. The idea was that this particular genetic variant might lead to increased sensitivity to glucocorticoids, which might explain the similarity between the phenotype and Cushing's syndrome. The study found no such effects.

There are two sets of related problems in hunting for obesity genes: one is implicit in the research paradigm and one is related to the methodology. If the genetic influence on the various forms of common obesity is based on multiple, polymorphic single genes—each with a small effect—that interact with other genes and with exposure to specific environmental factors, then current research strategies seem destined to fail. When research focuses on the relation between single genes and obesity and fails to control for other genes and environmental exposures, neither of which have been clearly identified, then both experimental and observational studies have little chance of identifying the pertinent genes.

The other set of problems derives from the risk of false positive results and false negative results. These problems are inherent in the low frequency of genetic variants, in the study populations, in the sampling of these populations, and in the measuring of the various forms of obesity and their presumed pathogenic mechanisms.

An extreme example of these problems is found in the discrepant results of two studies: the paper by Rosmond et al[10] and an earlier paper by Lin et al.[11] Both papers report on the same single gene polymorphism. Rosmond et al found no evidence that it is related to obesity but Lin et al found that the polymorphism was associated with an almost absolute risk of obesity.

It is not clear what would be the most effective way to proceed. The pressing need for progress is obvious in view of the continuing worldwide obesity epidemic and the complications of obesity, such as type 2 diabetes, hyperlipidaemia, hypertension, and eventual cardiovascular disease. One way forward might be to conduct controlled human experiments by manipulating environmental factors that are assumed to be pertinent, such as fat intake. Its effect on both gene expression and the function of gene products in people with different genetic variants may elucidate which genes contribute to common obesity.

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What is the optimal weight for cardiovascular health?

Debate about cut offs for obesity should not obscure need for population strategy

Although the health hazards of obesity have been clearly established, exactly where healthy weight ends and unhealthy weight begins is a matter of controversy.[1] Numerous studies have evaluated the association between weight and the metabolic abnormalities or diseases that occur in people whose weight is at the higher end of the scale, but comparatively few have examined these associations in people who fall into the lower or middle range of being overweight.

In the January issue of the *European Heart Journal*, Ashton and colleagues investigated the relation between body mass index (calculated as weight (kg)/(height (m)^2) and several established risk factors for coronary heart disease using a cross-sectional survey of 14 077 apparently healthy women aged 30 to 64 years.[2] Ashton et al found that as the women's body mass index (BMI) increased from <20 to >30, blood pressure also increased significantly, as did concentrations of total cholesterol, low density lipoprotein (LDL) cholesterol, apolipoprotein B, fasting triglycerides, and fasting blood glucose. Concentrations of high density lipoprotein (HDL) cholesterol and apolipoprotein A I decreased. Using a modified version of the Framingham heart study's algorithm for predicting the risk of coronary heart disease, the investigators showed that the estimated 10 year risk of coronary heart disease also increased significantly in a dose-response fashion as BMI increased from <20 to >30.

Ashton et al's data are consistent with several previous studies of body mass index and metabolic risk factors for coronary heart disease in comparatively lean and apparently healthy adults in diverse populations,[3–5] and thus have important implications. Firstly, they

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provide mechanistic support for the direct, linear association between BMI and coronary morbidity and mortality that has been observed in prospective cohort studies in Western populations.[1 6 7] Secondly, they suggest that the adverse metabolic consequences of adiposity may exist on a continuum, and that even small increases in body weight in the lower to middle range of the BMI distribution (<25) may translate into important increases in the long term risk of coronary heart disease.

Several analyses of morbidity have also found a direct association between the "normal" BMI range (18.5 to 25), the typical 5-10 kg weight gain that occurs during adulthood in Western populations, and increased risks of hypertension,[1 8] type 2 diabetes mellitus,[4] and myocardial infarction.[6] In a prospective study of over 100 000 nurses aged 30-55 in the US, for example, the relative risk of coronary heart disease among women who were compared with those with a BMI of <21 was 1.19 for women with a BMI of 21 to 22.9, 1.46 for women with a BMI of 23 to 24.9, and 2.06 for women with a BMI of 25 to 28.9.[6] Furthermore, among women with a body mass index <25, the amount of weight gained after the age of 18 remained a strong predictor of the risk of coronary heart disease. The association between weight and the risk of type 2 diabetes was even stronger: women with a BMI of 23 to 23.9 had a 3.6-fold increase in risk when compared with women with a BMI of <22.[9]

Although most studies of weight and metabolic risk factors for coronary heart disease have been conducted among Western populations, a recent study of 1610 rural Chinese peasants found that blood pressure, total cholesterol, LDL cholesterol, triglycerides, and blood glucose concentrations increased significantly as BMI increased from <18 to >24, and concentrations of HDL cholesterol decreased.[5]

Taken together, these data suggest that large variations exist in terms of metabolic risk factors for coronary heart disease and long term health risks even among people who fall into the "healthy" range of the BMI. What, then, is the optimal BMI range? Data from Ashton and colleagues suggest that for middle aged women a healthy BMI is <22.[2] These investigators pointed out, however, that they would not recommend a BMI cut-off point of 22 when trying to prevent coronary heart disease because the BMI does not discriminate between muscle and fat mass, and BMI alone is not a good indicator of fat distribution. Given that abdominal fat may increase the risk of coronary heart disease and type 2 diabetes more than fat in the hip or thigh does,[1] the addition of waist circumference to BMI may improve the prediction of risk of heart disease. Still, although BMI is an imperfect surrogate for adiposity and does not provide information about regional fat distribution, it is a simple and reliable measure of overall obesity that has been independently and consistently associated with several clinical endpoints.[1 8 10]

More than 50% of adults in the United States and United Kingdom are overweight, putting them at increased risk of hypertension, dyslipidaemia, type 2 diabetes, coronary heart disease, stroke, and other chronic disorders. In many developing countries, excess weight and related disorders now rival malnutrition as major public health problems.[11] Recognising this worldwide trend as an epidemic is an essential first step towards developing and evaluating public health interventions. Publications from the World Health Organization and the US National Heart, Lung, and Blood Institute offer guidelines for identifying, evaluating, treating, and preventing obesity.[1 11] Although both use BMI to classify individuals as overweight or obese, BMI should not be the sole indicator of weight related health. The results of Ashton et al's study and other studies suggest that some individuals with a BMI <25 may be considered overweight, and thus other indicators, such as abdominal adiposity or metabolic factors, must be assessed.

From a public health perspective, we must go beyond debating the best cut-off point for unhealthy weight. Primary prevention efforts, as advocated by the World Health Organization, should focus on the mean BMI and the shape of the curve for specific populations; strategies should be fashioned to correct underlying societal and environmental causes of weight gain in populations. A population based approach must target the entire population—from young people to older adults—through educational programmes that promote caloric balance through exercise and proper diet. Over the past two decades, the national cholesterol education programme of the US National Heart Lung, and Blood Institute has been a key element in lowering the mean concentrations of plasma cholesterol among American adults. An anti-obesity initiative using this successful programme as a blueprint could begin to quell the current worldwide epidemic of excess weight.

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